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Recent Progress in Histamine H₃ Receptor Chemistry

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1. INTRODUCTION

It has been over twenty years since the pioneering work of Arrang and co-workers demonstrated that histamine inhibited its own release from rat brain cortical slices via a novel receptor that is pharmacologically distinct from both the H₁ and H₂ receptors [1]. It is now well recognized that this third histamine receptor, the H₃ receptor, is a G-protein coupled receptor that functions both as an autoreceptor, controlling the release of histamine from histaminergic neurons, as well as a heteroreceptor, controlling the release of other neurotransmitters such as serotonin and noradrenalin. In the intervening years since the discovery of the H₃ receptor, considerable effort has gone into preparing novel H₃ receptor ligands and the field has evolved from one dominated by imidazole-derived analogs with their attendant pharmacokinetic and toxicological issues, to one in which there are now several classes of non-imidazole compounds. Additionally, the potential therapeutic utility of these molecules in the treatment of disease, particularly CNS related disorders, is now starting to be tested in human clinical trials. The goal of this report is to update the current state of the field of H₃ receptor medicinal chemistry.

2. NON-IMIDAZOLE H₃ RECEPTOR ANTAGONISTS

The imidazole analog thioperamide, 1, was the first selective H₃ antagonist identified [2], and most of the early literature in the field described compounds that were

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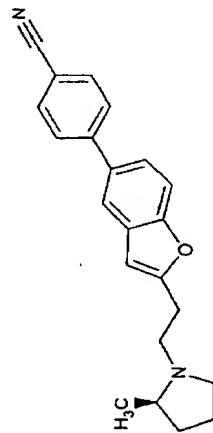
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ex. 11

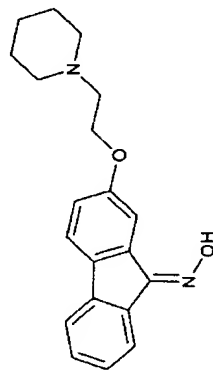
NC(=O)N1CCN(CC1)CCOCC2=CC=C(C(=O)C3CC4=CC=CC=C4C3=O)C2CN(C)[C@H]1CCCN1CCOC2=CC=C(C=C2)C3=CC=C(C=C3)C#N

This lead structure was further optimized. In an attempt to prepare more rigid analogs and thus potentially improve the pharmacokinetic and selectivity profiles of the series, benzofuran analog **7** was obtained by cyclization of the alkyl ether chain back onto the central phenyl ring [11]. Compound **7** is a potent ligand for the human and rat H_3 receptors ($K_i = 0.45$ and 3.22 nM, respectively) and displays excellent brain concentrations after i.v. dosing (brain/plasma > 30). This compound is reported to be in Phase I clinical trials for the treatment of cognition related disorders.

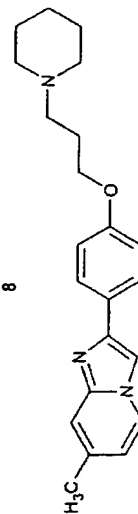


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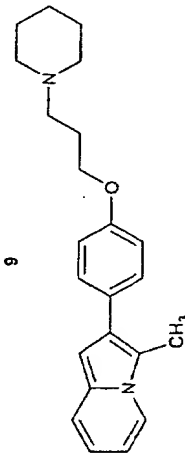
This privileged H_3 pharmacophore has appeared in several other series of H_3 receptor ligands. Oxime 8 is structurally related to 6 in that the biphenyl moiety of 6 is now linked via a five-membered ring. In this case, the Z-oxime is essential for good H_3 activity ($K_i = 65$ nM). The E-oxime is approximately tenfold less active [12]. Imidazopyridine 9, which was also derived from a lead identified via high throughput screening, is a potent ligand for the human H_3 receptor ($K_i = 2$ nM) with good selectivity over the H_1 , H_2 , and H_4 receptors as well as more than 50 other biogenic amine and neuropeptide receptors. Compound 9 also displayed good oral pharmacokinetics after dosing in the rat [13]. Sequential removal of each of the nitrogen atoms of 9 gives either an indolizine or indole analog, respectively [14]. The indolizine analogs were more potent than the corresponding indoles with the 3-methyl analog 10 being equipotent to 9 ($K_i = 2$ nM).



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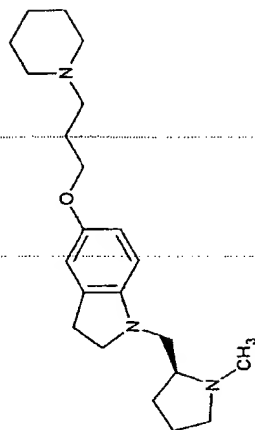


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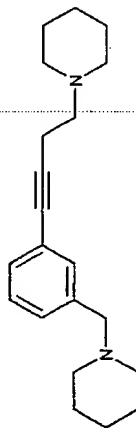
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A number of other groups have also reported variations on this theme. For example,

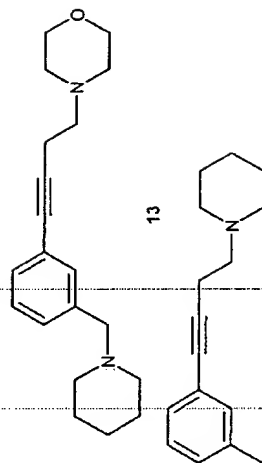


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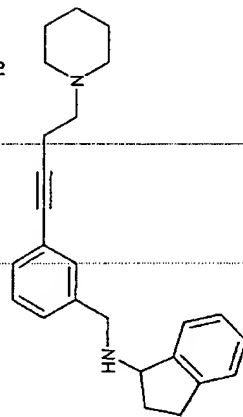
Not all non-imidazole H_3 antagonists fit this pharmacophore. A structurally related but novel series of piperidine alkynes exemplified by structure 12 has been prepared [16]. In this case an alkyne moiety has replaced the ether linker. Optimum binding activity seems to reside in those analogs with a basic tertiary amine on the 4-position of the butynyl chain. For example, compound 12 ($pK_a \approx 10.1$) binds to the H_3 receptor with subnanomolar affinity ($K_i = 0.8$ nM). The corresponding morpholine analog 13 ($pK_a \approx 7.4$) is a significantly weaker ligand ($K_i = 15$ nM). While the 4-position of the butynyl group seems to be sensitive to substitution, the 3-position of the central phenyl ring is more tolerant. For example, the left-hand piperidine of 12 can be replaced with the much bulkier indanyl amine as in 14 and still retain good binding affinity ($K_i = 1.3$ nM).



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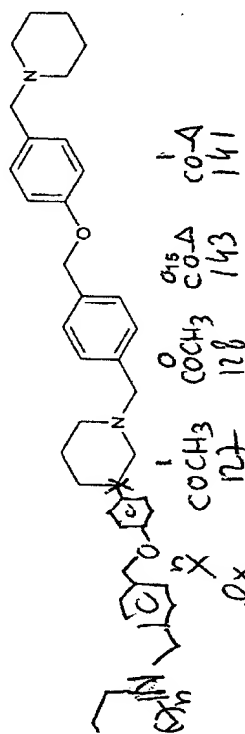
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Pseudo-symmetric analog 15 represents another series of unique non-imidazole

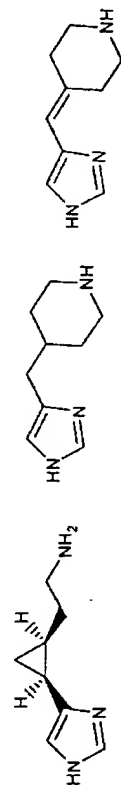
($K_i = 2.8$ nM) although it was relatively weak *in vivo* in the mouse when dosed orally ($ED_{50} = 9.6$ mg/kg).



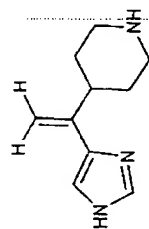
3. IMIDAZOLE DERIVED H_3 RECEPTOR AGONISTS AND ANTAGONISTS

3.1. Selective H_3 receptor agonists

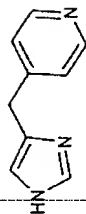
Although there has been noteworthy progress in the discovery of non-imidazole H_3 receptor antagonists, significant interest still exists in imidazole based analogs as well. The discovery of the histamine H_4 receptor which shares an overall 43% identity homology to the histamine H_3 receptor has rekindled interest in discovery of highly selective H_3 receptor ligands [18]. Recently, a cyclopropane-based conformationally restricted analog of histamine, **16**, was found to be a potent H_3 receptor agonist which exhibits very good binding affinity ($K_i = 1.3$ nM) and functional activity ($EC_{50} = 10$ nM) but has virtually no effect on the H_4 receptor [19]. SAR investigations on imineprip **17** ($pK_i = 9.32$; $pEC_{50} = 9.88$), a potent H_3 receptor agonist of moderate selectivity (46 fold favoring the H_3 receptor), resulted in the identification of olefin analogs **18** and **19** which exhibit decreased affinity and functional activity at the H_3 receptor ($pK_i = 8.23$ and 8.40 ; $pEC_{50} = 8.50$ and 8.63 , respectively) but increased selectivity for the H_3 receptor over the H_4 receptor (300 and 700 fold, respectively) [20]. Alternatively, replacement of the piperidine ring of **17** with a 4-pyridine resulted in the discovery of a potent and highly selective H_3 receptor agonist, immethridine **20** ($pK_i = 9.07$, $pEC_{50} = 9.74$), which exhibits 300-fold H_3 receptor selectivity over the H_4 receptor [21]. In the search for novel H_3 receptor agonists, which lack a basic moiety in the side chain of the molecule in order to improve pharmacokinetic properties, a novel chiral carbamate **21** was prepared. Compared to BP294, a prodrug of (*R*)- α -methylhistamine, compound **21** was significantly more efficacious in all tissues investigated in the capsaicin-induced plasma extravasation models in rats ($ED_{50} = 0.07$ – 0.1 mg/kg p.o.) [21,22].



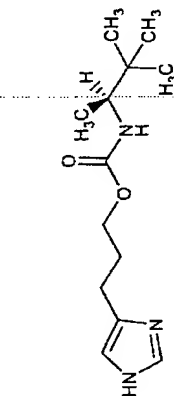
Recent Progress in Histamine H_3 Receptor Chemistry



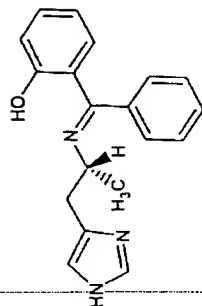
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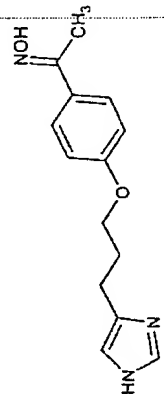
21 (S-)



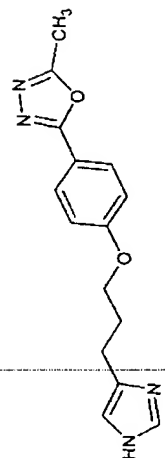
22 (BP 2.94) (R-)

3.2. Imidazole H_3 receptor antagonists

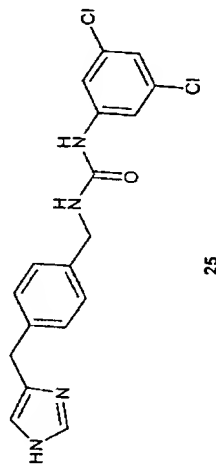
The proxifan class, compounds containing an imidazole heterocycle connected by a three-carbon alkyl chain to a *para*-substituted phenyl ether moiety, was previously reported to contain numerous potent and orally active H_3 antagonists, e.g., ciproxifan [**5**] ($K_i = 0.49$ nM; $ED_{50} = 0.14$ mg/kg p.o.) and imoproxifan (**23**) ($K_i = 0.26$ nM; $ED_{50} = 0.034$ mg/kg p.o. in mice) [23,24]. Recent work on the design of novel heterocyclic proxifan analogs has led to the identification of oxadiazole derivatives which displayed reduced potencies compared to those of ciproxifan and imoproxifan, but retain high *in vivo* efficacies, e.g., compound **24** ($K_i = 13$ nM; $ED_{50} = 0.57$ mg/kg p.o.) [25]. In an effort to discover a novel and selective H_3 antagonist that can be used in combination with an H_1 antihistamine for the treatment of nasal congestion, a novel series of H_3 receptor antagonists was prepared by incorporating urea and carbamate linkers to the 4-benzyl-(1*H*-imidazole-4-yl) template. The urea **25** is a potent H_3 antagonist ($K_i = 4$ nM) and it demonstrated excellent oral plasma levels in the rat (AUC = $18.1 \mu\text{g h/ml}$ at 10 mg/kg p.o.) and monkey (AUC = $12.6 \mu\text{g h/ml}$ at 3 mg/kg p.o.) [26].



23 (imoproxifan)



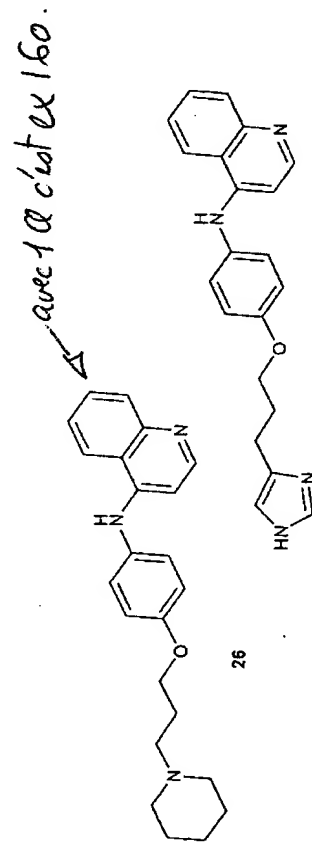
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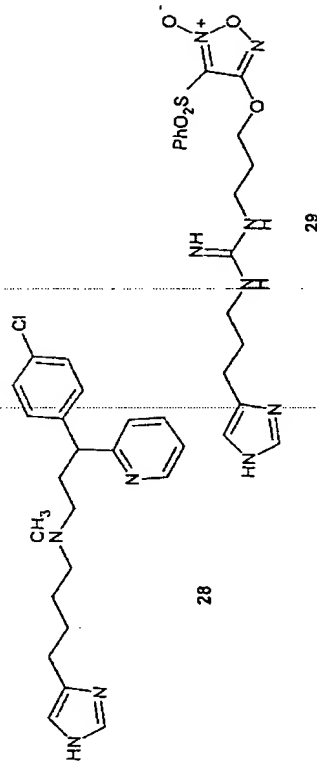
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4. HISTAMINE H₃ ANTAGONISTS WITH A DUAL MODE OF ACTION

Three series of compounds which combine H₃ antagonism and another pharmacological profile in one molecule were recently reported. In contrast to the combined application of two molecules, these hybrid molecules have the advantage of a single pharmacokinetic and toxicological profile. In search of novel ways to enhance histaminergic neurotransmission in the central nervous system, a novel class of aminoquinoline histamine H₃ receptor ligands was developed that simultaneously possessed strong inhibitory activity on the main histamine metabolizing enzyme, histamine N-methyltransferase (HMT) as well as H₃ antagonist activity. Non-imidazole 26 (K_i (H₃) = 0.09 nM; IC_{50} (HMT) = 51 nM) and imidazole 27 (K_i (H₃) = 4.1 μ M; IC_{50} (HMT) = 24 nM) exhibit dual H₃ antagonistic and HMT inhibitory activity [27,28]. Combining the first generation H₁ antihistamine chlorpheniramine with H₃ ligands of the alkylamine type has led to the discovery of dual ligands of the H₁ and H₃ receptors, e.g., 28 (K_i (H₁) = 7 nM; K_i (H₃) = 15 nM). Compounds such as 28 may be useful for the treatment of allergies and nasal congestion [29]. Nitric oxide (NO) is a recently discovered endogenous messenger. There is strong evidence that furoxan system (1,2,5-oxadiazole, 2-oxide) is able to release NO under the action of thiol cofactors [30]. Consequently, a series of H₃ antagonists endowed with NO-donor properties were designed by coupling the H₃ antagonist SKF91486 with the NO-donor furoxan moieties. Although behaving only as a weak partial H₂ agonist, compound 29 (pA_2 (H₃) = 7.02; pD_2 = 5.28) was able to trigger a dual NO-dependent muscle relaxation and H₃-antagonistic effect on guinea-pig ileum [31].



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28

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Anti-Resorptive and Anabolic Bone Agents

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1. INTRODUCTION

Osteoporosis is a disease characterized by an increased risk of bone fractures that result from reduced bone mass and bone strength [1-3]. In humans, bone mass is maintained or increased through the balancing actions of continuous bone resorption and deposition. In healthy individuals, bone mass reaches a peak during early adulthood, and then begins to slowly decline with advancing age. Women, who generally have lower peak bone mass than men, experience a more rapid loss of bone following menopause. The accelerated loss of bone material is associated with an increasing risk of fracture over time. In the United States, 10 million persons are estimated to have osteoporosis, a total of 34 million have low bone mass, indicating increased risk of disease. The estimated national direct expenditure for osteoporosis and associated fractures in 2000 was 17 billion USD.

Osteoporosis therapy seeks to maintain or increase bone mass and strength so that fracture risk is reduced. This can be done by decreasing the rate of bone resorption, increasing the rate of bone deposition, or by a combination of both actions. Several novel

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